Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

optimal dosage and duration of imatinib treatment, the best time to start treatment after symptom onset, and the possible interactions when taken in combination with other drugs, such as dexamethasone (given to 276 [72%] of 385 patients in the study[8]), which could decrease exposure to imatinib due to its CYP3A4-inducing action.[9]

Since the pandemic started approximately one and a half years ago, we have learned that we should temper our enthusiasm on receiving initial data for a potentially beneficial treatment in COVID-19, especially after witnessing unexpected results of randomised trials of previous therapeutic approaches involving sufficiently large numbers of patients. This fact will undoubtedly be conditioning our view of new therapies against SARS-CoV-2 infection until the inherent uncertainties can be resolved. In other words, we have also learned not to succumb to so-called optimism bias[10] as easily as we did at the beginning of this unprecedented global health crisis. It is precisely this evolving view that calls again for a thoughtful judgment of promising data from well known drugs repurposed as treatments for new challenges, such as COVID-19.

DB-B is the principal investigator of a non-sponsored randomised trial investigating the role of imatinib and baricitinib in patients with COVID-19 (NCT04346147); AM-O, AIF-S, JGdT and JVSM-L are co-investigators in this project.

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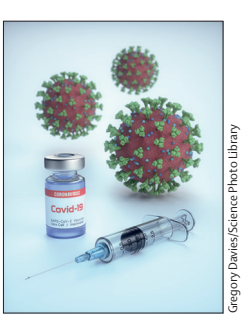
Battling COVID-19-related mortality: from a fight for ventilators to a cry for oxygen

COVID-19 has caused hundreds of thousands of intensive care unit (ICU) admissions worldwide, and this number continues to increase rapidly as of mid-May, 2021, particularly in countries that are lagging behind in vaccinating vulnerable individuals. Meanwhile, ICU clinicians and researchers have learned a lot about COVID-19, in part through the many epidemiological studies of this disease. However, most reports have, so far, originated in high-income countries.[1–5]

In *The Lancet Respiratory Medicine*, Elisa Estenssoro and colleagues[6] report on a prospective study (SATICOVID) of ventilation characteristics and outcomes in invasively ventilated patients with COVID-19 in Argentina, an upper middle-income country. In their cohort of 1909 patients in 63 ICUs, lung-protective ventilation with a low tidal volume and high positive end-expiratory pressure (PEEP) was frequently used, and respiratory system compliance was low (median 36 mL/cm H_2O [IQR 29–44] on day 1) with little variation—similar to the findings of studies in high-income countries (table). Even a labour-intensive strategy such as prone positioning was used often (in 1176 patients [61·6%]). Age, D-dimer concentration, disease severity, ratio of partial pressure of arterial oxygen to fractional inspired



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	SATICOVID (n=1909)[6]	PRoVENT-COVID (n=533)[1]	Ferrando et al (n=742)[2]	REVA network (n=4244)[3]	Grasselli et al (n=301)[4]	Cummings et al (n=257)[5]
Country	Argentina	Netherlands	Spain	France, Belgium, and Switzerland*	Italy	USA
Period of inclusion	March–October, 2020	March–April, 2020	March–June, 2020	February–May, 2020	March, 2020	March–April, 2020
Patient characteristics						
Age, years	62 (52–70)	67 (59–73)	64 (56–71)	64 (54–71)*	63 (55–70)	62 (51–72)
Sex						
Female	615 (32%)	136 (25%)	236/740 (32%)	1085 (26%)	69 (23%)	86 (33%)
Male	1294 (68%)	417 (75%)	504/740 (68%)	3159 (74%)*	232 (77%)	171 (67%)
PaO_2/FiO_2, mm Hg	160 (111–218)	159 (129–200)	120 (83–177)	154 (106–223)	124 (89–164)	103 (82–134)
Ventilatory variables at day 1						
Tidal volume, mL/kg predicted bodyweight	6·1 (6·0–7·0)	6·3 (5·7–7·1)	6·9 (6·3–7·8)	6·1 (5·8–6·7)	7·0 (6·3–7·6)	6·2 (5·9–7·2)
PEEP, cm H_2O	10 (8–12)	14 (11–15)	12 (11–14)	12 (10–14)	13 (10–15)	15 (12–18)
Respiratory system compliance, mL/cm H_2O	36 (29–44)	32 (26–40)	35 (27–45)	33 (26–42)	41 (33–52)	27 (22–36)
Outcomes						
Duration of ventilation, days	13 (7–22)	13 (7–22)	14 (7–24)	11 (7–17)	..	18 (9–28)
Hospital mortality	1101 (58%)	210 (42%)	..	1173 (37%)	..	101 (39%)
28-day mortality	966 (51%)	186 (35%)	241 (32%)	1019 (30%)	93 (36%)	..

Data are n (%) or median (IQR), unless otherwise specified. PEEP=positive end-expiratory pressure. *Includes patients not receiving invasive ventilation.

Table: **Comparison of patient characteristics, ventilation management, and outcomes in studies of invasively ventilated patients with COVID-19**

oxygen (FiO_2), driving pressure, need for vasopressors, and arterial pH all had an independent association with the primary outcome—confirming that which has been described in previous cohorts in high-income countries.

Without doubt, the COVID-19 pandemic has resulted in a unique situation for critical care researchers. ICU teams have been confronted with numbers of patients with acute respiratory distress syndrome (ARDS) over a period of months that would normally be seen over periods of years, and this increase in patient numbers has allowed the completion of studies far larger than previously would have been possible. The research community quickly learned that ARDS due to COVID-19 is a fairly homogeneous disease. In less than a year, two decades of ARDS research could be repeated. And while there will certainly be many more reports to follow, the results of these research efforts have been somewhat disappointing—mortality remains high, and much of what we knew in the pre-COVID era has only been confirmed. The study from Argentina, however, shows something striking: despite all the similarities in terms of care and factors associated with mortality, outcome was much poorer—all-cause in-hospital mortality was 57·7% (1101 of 1909 patients)—than in cohorts in the well-resourced ICUs of high-income countries. How might this be explained?

The high mortality in patients with COVID-19 in Argentina does not stand alone—a similar mortality rate (1028 [58·2%] of 1765 mechanically ventilated patients) has been reported in a large study from Brazil,[7] another upper middle-income country. In that study, a remarkable temporal change in outcome was found alongside the increased use of measures to prevent invasive ventilation. Indeed, with an increased use of non-invasive respiratory support such as continuous positive airway pressure and high-flow nasal oxygen (HFNO), mortality rates dropped from 18% to 10%. In this context, it is important to note that non-invasive ventilation and HFNO were rarely used in the cohort from Argentina (in 73 [3·8%] and 144 [7·5%] of 1909 patients, respectively) and it remains unclear whether there was a temporal change (ie, an increase) in their use.

However, the rare use of non-invasive ventilation and HFNO cannot explain the difference in mortality compared with other cohorts—for instance, a study in the Netherlands consisting only of invasively ventilated patients showed a much better outcome, with

an in-hospital mortality of 42% (210 of 496 patients).[1] A salient factor that had an association with mortality in the study from Argentina was intubation outside the ICU (hazard ratio 1·37 [95% CI 1·10–1·71]). Delayed admission due to unavailability of ICU beds is a major problem in many South American countries,[8] and a shortage of beds might have been an even bigger problem during the surge of patients with COVID-19. Despite the quality of care provided by staff on the ward, delayed admission to the ICU is associated with worsening of organ dysfunction and increased mortality rates.[9]

These findings show the real distinction between COVID-19-associated ARDS and ARDS due to other causes—it is the sheer numbers of patients that make the difference. Health-care systems had to function, and still are functioning, under immense stress, with shortages of beds and ventilators causing delays and denials, all resulting in massive numbers of deaths in many countries. Not surprisingly, the world fought back, with many initiatives to develop simpler and cheaper ventilators, many of which got approval for emergency use.

Will the hard-fought wisdom that ventilation can be avoided with increased use of alternatives, such as HFNO, be a game changer? The answer might be a yes in some settings, but certainly a no in other places. HFNO can be applied with an ample supply of oxygen, some of which is wasted. With invasive ventilation, oxygen consumption is between 8 and 12 L/min (at an FiO_2 of about 70–80% and a minute volume of about 12–15 L/min, which is not unusual in invasively ventilated patients with COVID-19); with HFNO, oxygen consumption is 36 L/min or more (at an FiO_2 of 60% and an air flow of 60 L/min, which are often the settings at the start of treatment but are frequently higher in sicker patients). Thus, HFNO might cause or exacerbate the problem of a lack of piped oxygen, of oxygen cylinders that are too small, or of simply having too little oxygen. This all has caused oxygen shortages—and distressing scenes—in the USA, Brazil, and India, and probably worldwide. Oxygen concentrators do not solve the problem, as most concentrators do not deliver more than 10 L/min; modern and more expensive versions do better, but they remain insufficient because they can produce only up to 15 L/min.

When you have little, you need to use less to serve more—this is true for ventilators, and it is even more true for oxygen. Proper use of ventilators can save lives and when ventilators run short, patients should only be connected to them when there is a good chance of survival. Proper use of oxygen also saves lives and when oxygen is restricted, more emphasis should be put on the use of close-fitting, low-flow systems and on strategies that reduce the need for high FiO_2, such as positive airway pressure or (awake) prone positioning.[10] The use of HFNO should perhaps be forgone under these circumstances.

We declare no competing interests.

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